EVALUATION OF RESEARCH STRATEGIES FOR INVESTIGATION OF HEALTH EFFECTS OF AIR POLLUTION*

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SPEAKING last, we have the advantage or disadvantage of repeating some of the previous discussants' comments.

Dr. Herbert Schimmel has painstakingly and carefully studied the acute effects of air pollution on mortality in New York City. He has candidly pointed out many possible sources of error in his study and has applied some powerful statistical techniques to attempt to correct these errors.

While we recognize that linear regression is a powerful tool, we have serious reservations about how it has been used in many epidemiologic studies that relate health indices to pollution levels. The problems arise partly from the scientific hypotheses that one is led to make by the nature of linear regression and partly by problems with the data themselves, both for the dependent variable (health) and the independent variables (pollution and weather). Although we comment on various features of Dr. Schimmel's studies alone, we suggest that many other studies, often reaching conclusions diametrically opposite to his, have the same weaknesses.

Studies of this kind basically seek to answer such questions as: How harmful to health is some specific pollutant? What regulatory measures are desirable as a result? These questions have important social consequences,

*Presented as part of a *Symposium on Environmental Effects of Sulfur Oxides and Related Particulates* sponsored by the Subcommittee on Public Health Aspects of Energy of the Committee on Public Health of the New York Academy of Medicine and held at the Academy March 23 and 24, 1978.

This study was supported by Grant No. 00899 from the National Institute of Environmental Health Sciences, Durham, N.C., and by SIMS Study on Statistics and Environmental Factors in Health under the auspices of the SIAM Institute for Mathematics and Society. New Canaan, Conn.

and we need to be sure the methods used to answer them deserve our fullest confidence.

The specific questions raised in Dr. Schimmel's papers are the following:

1) Is sulfur dioxide an injurious pollutant at the levels encountered in the air of New York City?

2) Does sulfur dioxide serve as an indicator of air quality?

3) Should sulfur dioxide standards be relaxed or entirely abandoned?

The first two questions we infer from the conclusion to his paper,[2] which we quote: "Our statistical studies. . . suggest that SO_2 is not only serving as an indicator of air quality, but also that SO_2 is not an injurious pollutant, at least at the ambient levels encountered in New York City in the 1960's."

The third question we infer also from the conclusion section of the paper:[2] "In light of our immediate study and the available health information, it would appear that the SO_2 standards should either be relaxed or abandoned entirely."

Dr. Schimmel's answer to the first question mentioned above, obviously the basis for the answer to question 3, is expressed in his conclusion as to the results of his statistical study: adverse health effects arising from pollution "are associated principally (80%) with the particulate measure (Smoke Shade) and only a small fraction (20%) with the SO_2 measure."[2,5]

After review of Dr. Schimmel's papers, [1-6] the state of the data, and the scientific hypotheses that underlie his analysis, we conclude that the limitations of the approach are so severe that they fail to support his conclusions. Specifically, his studies do not permit us safely to draw the conclusion that sulfur dioxide in urban air is not injurious to health, nor that particulates are the real culprits in air pollution, nor that their health effects are negligible, nor can we conclude that sulfur dioxide is an indicator of air quality. It follows also that we would certainly not, on the basis of this series of papers, recommend the relaxation or abandonment of sulfur dioxide standards.

We are here concerned with why studies of this kind do not justify such conclusions. In particular, we shall stress that the scientific problem is more complex than one might infer from Dr. Schimmel's analyses. Admitting that this might leave us without a solid scientific answer to the questions—How harmful is sulfur dioxide to health? Should the burning of higher sulfur fuels than currently allowed be permitted?—we submit that it is better to admit the gaps in our scientific knowledge than to draw conclusions from faulty and incomplete analyses.

Our criticisms may be classified into three categories:

1) Problems with the specification of the pollution variables

2) Problems with meteorological variables which directly affect health variables and interact in a complicated way with the pollution variables

3) Problems with the health indices, the dependent variables in these studies

Most of the points we raise have been raised before, some in our own publications,[7-16] some by others,[17-20] and some by Dr. Schimmel himself.[1-6] We bring them together to make a comprehensive evaluation of the scientific issues involved in the use of multiple linear regression to relate acute health effects to ambient levels of one or two pollutants, and we use his methodology as an example.

Pollution Variables

Serious experimental errors in measurement of pollution variables by usual aerometric procedures are widely recognized and often exceed 100% at ambient levels commonly encountered in New York City air.

We quote a critical report on The Community Health and Environmental Surveillance System (CHESS) of the U.S. Environmental Protection Agency, prepared for the Subcommittee on Special Studies and the Subcommittee on the Environment and the Atmosphere of the U.S. House of Representatives Committee on Science and Technology:[21]

> There were too many inconsistencies in the data and too many technical problems that resulted in large data uncertainties or errors associated with aerometrics for this program to provide quantitative support for policy decisions. The $25\mu ug/m^3$ lower sensitivity limit of the method used for most sulfur dioxide measures coupled with the large error band on all measurements (possibly exceeding 100%). . . make most of the numbers presented in the CHESS monograph unusable.

Poor reliability of sulfur dioxide measurements under the more nearly ideal conditions of collaborative testing raises serious questions about the use of sulfur dioxide readings from aerometric stations in studies of the acute health effects of air pollutants. It should be recalled that measurement errors become more serious as mean levels of ambient sulfur dioxide decrease. This is particularly serious with the method used at the Harlem station. The conductrimetric method is highly unreliable at the low level of sulfur dioxide which has prevailed in recent years.

A series of collaborative tests performed by the Environmental Protection Agency (EPA) using the reference pararosaniline method to measure sulfur dioxide in the test atmosphere drew the following conclusions:

For 2 single observations by the same analyst, differences of 20% or more may not be detected at an SO_2 concentration of 300 $\mu g/m^3$ (approximately 0.1 ppm).

The method cannot detect differences of less than 20% between single observations of two laboratories in the range of 0 to 1000$\mu g/m^3$. At a level of 100 $\mu g/m^3$ the difference of 100% is not detectable [present levels of SO_2 in New York City air are approximately 100$\mu g/m^3$].

An extensive report by the EPA describes in detail the great sensitivity of this method to temperature. Let us remember that these studies refer only to the reliability of two or more measurements performed on a single sample of air.

No measure of compounds of sulfur other than sulfur dioxide are available from the New York City aerometric station, and are therefore not included in the regression analysis. But this study and others of its kind undertake to answer whether sulfur dioxide is an injurious pollutant at levels encountered in the air of New York City and whether reduction in the sulfur content of fuel results in reduction of health effects attributable to high levels of sulfur in fuel combustion. Toxicological studies[23-25] have shown that the oxidation products of sulfur dioxide (sulphuric acid and sulfates) are more likely to have harmful health effects than sulfur dioxide itself. It might be argued that in the absence of direct data on air concentrations of other sulfur compounds we might use sulfur dioxide concentration to indicate their probable concentrations. However, poor short-term correlations are found between sulfur dioxide and the few other sulfur compounds that have been studied; most such compounds have not yet been studied extensively in this way, nor have all the end-products of sulfur dioxide even been chemically identified.[19] The kinetics of the chemical transformation of sulfur dioxide into its end products under conditions encountered in urban atmospheres are not well understood, but are likely to depend on many such meteorologic and pollution variables as humidity, temperature, sunlight, oxidant, and metal concentration. Toxicologic studies have demonstrated that individual sulfates have widely different biological activities. Further, the biological activity of sulfates markedly depends on particle size and on the presence of such other substances as trace elements, which in turn will be expected to depend on meteorologic factors both current and at the time of formation. These compounds are currently believed to have adverse health effects associated with stationary combustion of fossil fuels.

The following quotations from a National Academy of Sciences report on sulfur oxides brings out some of the complexities of the problem.

> Within a large region such as the northeastern United States, particulate sulfate concentrations in the atmosphere are related to regional emissions of sulfur dioxide, which is converted to sulfates after emission. Because sulfur dioxide and sulfates may be transported long distances before being removed from the atmosphere, and because during the transport period there is conversion of sulfur dioxide to sulfates, there is not always a close relationship between ambient concentrations of the sulfates and emissions of sulfur dioxide in the immediate vicinity. For cxample, in some rural areas in the Northeast where there are comparatively low sulfur dioxide emissions and low ambient sulfur dioxide levels, ambient sulfate concentrations are substantially above background levels. Adverse consequences to health from combustion of sulfur-containing fossil fuels cannot be simply ascribed to any one sulfur oxide acting alone. (The term oxide is used to mean the family of compounds including sulfur dioxide, sulfuric acid, and various sulfate salts. Sulfur dioxide is the main sulfur oxide directly emitted by fossil fuel combustion). Sulfur dioxide itself appears unlikely to be the direct cause of excess morbidity and mortality associated with stationary source fossil fuel combustion. However, levels of sulfur dioxide close to the current ambient air quality standards may be responsible for deleterious effects on health when inhaled in combination with respirable (very small) particulate matter or the oxidant air pollutant ozone. Oxidation products of sulfur dioxide, including sulfuric acid and suspended particulate sulfates, are more toxic than the parent compound and appear likely to be responsible for a substantial portion of adverse effects on health associated with stationary source combustion of fossil fuels.
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> The specific chemical species responsible for toxicity have not been determined. This hampers the exact determination of the morbidity and mortality from sulfur oxides. The use in epidemiological correlations of monitoring data for total suspended particulates and sulfur dioxide has undoubtedly led to imprecision inasmuch as these two measurements do not directly assay the causative agents. It is possible that the use of these indicators may have led to underestimation or overestimation of the health consequences of sulfur oxide or respirable particulate matter, but most likely underestimation.[19]

Measurement of the coefficient of haze (Smoke Shade) is a gross average index of particulates that fails to give any information about particle size or chemical composition—factors known to be of great importance in producing physiological effects.

Dr. Schimmel's studies have failed to examine the possibility that sulfur dioxide and particulates might have a synergistic effect on health. Such interaction, for example, could have been studied using as an explanatory variable the product of sulfur dioxide and particulate concentrations. No attention is paid to the possible direct influences on health of other pollutants, or as influences that may act synergistically, a possibility that is not a fanciful academic speculation.

The focus on sulfur dioxide as a pollutant has been critized because both animal and human laboratory experiments have shown that in isolation concentrations comparable to population-exposure levels in the United States produce no deleterious effects. However, Amdur [23] has shown that certain trace metals present in the atmosphere as water-soluble salts strongly potentiated response to sulfur dioxide.

Syngerism between ozone and sulfur dioxide has been demonstrated by Bates [26] in human subjects exposed to 0.3-0.4 ppm. of these gases. It seems that while ozone and sulfur dioxide do not react in dry air at low concentrations unless olefins are present, they are very likely to react in the moist atmosphere of the lung to produce sulfuric acid. Benzo-a-pyrene, a well known carcinogen, when inhaled by rats does not produce squamous cell carcinoma, but when a background level of sulfur dioxide is added (3.5 ppm. and 10 ppm.) to the benzo-a-pyrene mixture, squamous cell carcinoma is produced. [27]

These examples illustrate problems that arise because interactions between environmental variables prevent us from treating each of them independently of the others. Many more such interactions are known, and still many more are yet to be discovered. Most pollutants are chemically reactive, and the rates and extents of their reactions will depend on the chemical and physical state of the environment.

Outdoor air pollution at one aerometric station is used as the measure of individual exposure, although the people who live in the five boroughs of New York City spend different amounts of time indoors and outdoors, and engage in diverse activities when doing so.[22] Specifically, vulnerable groups in Dr. Schimmel's study are likely to spend the major portion of their time indoors. However, it is not plausible that indoor pollutant concentrations should vary in the same way as outdoor concentrations, nor is it plausible that, whatever the relation, it should remain the same from season to season; in winter, windows are closed, while the rest of the year they tend to be open except in the hot spells of summer, when some homes are air conditioned and some are not. Cigarette smokers in the household or the use of a gas stove can increase exposure to pollutants by several orders of magnitude.

On several occasions we have criticized studies that used a single, centrally located pollution-measuring station to represent the exposure of the entire metropolitan area.[8-12,14,15] As Dr. Schimmel has pointed out, the data of the 40-station New York City aerometric network were not available for the entire period that his study covers (1963-1976), and, even though available since 1968, considerable gaps exist in the coverage because of missing and erroneous readings, the absence of data for weekends, and so on. We recognize that his studies could not have been performed in the way he did them for the time covered unless he relied on the single central station, but the point at issue is how serious the errors are.

Dr. Schimmel, in his Appendix E, suggests methods to estimate the errors that result from the use of a single station, and concludes that the use of a single station tends to underestimate the effects on health in New York City, but he makes no quantitative estimate of the resulting error using the correlation coefficients we have published. (Average correlation coefficients between daily average readings at all pairs of stations of the New York City aerometric network calculated by season was 0.5 for sulfur dioxide and 0.4 for Smoke Shade and ranged from -0.8 to $+0.9$.) His conclusion appears to be that his calculated effects are lower bounds to the true effects, but he provides not way to guess how low the lower bounds are.

Dr. Merril Eisenbud's demonstration of a high (0.8) correlation coefficient of annual averages for sulfur dioxide between the central station and the city average over the period of Dr. Schimmel's study does not, of course, conflict with the fact that correlation coefficients for the daily averages, data used by Dr. Schimmel, are low and variable.

The use of linear regression when more than one independent variable exists is a straightforward extension of this approach when there is one independent variable. When the explanatory variables (two pollution variables and temperature) are correlated, as is the case here, the regression coefficients found are uncertain in meaning and fail to represent properly the actual relation between dependent and explanatory variables. Dr. Schimmel is aware of this but fails to estimate the shadow of uncertainty it casts on his conclusions.

Weather Variables

Few researchers have recognized the importance of weather and the complex nature of its relation to the other variables in their studies. From his first paper Dr. Schimmel has attempted to correct for the effect of weather, but we feel that the statistical techniques he has employed are inadequate to the problem. For example, in earlier analyses Dr. Schimmel et al. found that only temperature among a variety of meteorologic variables examined gave statistically significant correlations with mortality;[1] it was therefore decided to use mean daily temperature as the only weather variable requiring consideration. We submit that the role of meteorologic variables in this problem is more important and far more complex than Dr. Schimmel's choice of temperature as the only relevant variable would imply. Weather itself influences pollution variables. More fuel is used in very cold weather and, in very hot weather, for air conditioning; greater fuel use results in higher emissions of pollutants. How much of these pollutants remain in the ambient air is in turn influenced by wind speed, precipitation, and inversion height.

Turning now to temperature, the one meteorologic variable taken into account by Dr. Schimmel, we note that he has found that temperature correlates with both pollution and daily mortality, apparently accounting for about 25% of the variance in pollution, and from 10 to 50% of the variance in mortality. He therefore proposes to estimate the direct effect of pollution on health by first eliminating variations due to temperature. But does this not tacitly make a scientific hypothesis for which no justification is offered? Can we be confident that sulfur dioxide does not cause some substantial part of the effect attributed to temperature? Dr. Schimmel has found that mortality is positively correlated with temperature (after the removal of the slow rhythm components) even in winter. In this scientifically plausible without further explanation? Could it be that warmer days in winter are associated with lower wind speeds and therefore with higher levels of pollution? William Hodge[28] of the National Climatic Center has confirmed that wind speed in winter in New York City for 1973-1976 was indeed higher on colder days. This suggests that by controlling temperature in the manner used by Dr. Schimmel we may ignore a real effect of sulfur dioxide.

A further example of the complexity of the problem is seen when we examine relative humidity and its relation to pollution. A very high level of relative humidity may or may not be associated with precipitation; precipitation tends to cleanse the air of pollutants, but high levels of humidity without rain could be associated with high pollution levels. Increased humidity is known to accelerate the reaction between particulates and sulfur dioxide to form sulfates and sulfuric acid aerosols.

Weather itself has a distinct effect on health.[7] Not only temperature, but such variables as humidity, precipitation, and wind-speed, and such combinations as wind-chill factor are all likely to affect health indices. Their effects interact with each other: summer humidity associated with heat spells has a different effect from humidity in the winter, and high temperature is more of a stressor when associated with humidity. Weather may act synergistically with pollutants to produce adverse health effects. For example, synergistic toxicity between sulfur dioxide particles and humidity has been observed.[23]

Health Indices

The use of mortality rather than morbidity as an index of acute health effects is a questionable procedure. People dying of cardiac or respiratory diseases or of cancer die from long-term chronic and even life-time conditions, and interaction with short-term episodes is only a peripheral factor at the time of death. In contrast, such morbid conditions as asthma and certain other respiratory conditions are those most plausibly expected to be exacerbated during pollution episodes and are rarely a direct cause of death.

The use of mortality in the general population, rather than morbidity within sensitive groups such as asthmatics or victims of chronic bronchitis, has been previously criticized. Dr. Schimmel's current separation of the target population into age, sex, and race categories and by diagnostic categories mitigates this difficulty to a small extent, but still fails to focus on those who might be most strongly affected by short-term environmental changes but are not yet moribund. Such an approach is likely to swamp significant effects in the more sensitive and smaller subgroups.

Alternative Strategies

Dr. Schimmel has recognized and discussed many of the criticisms we have made of his methodology, both in this and in earlier papers in the section on methodology of the paper before us. However, although he acknowledged them, he has not adequately eliminated or minimized their influence, nor has he successfully estimated their quantitative effects on his conclusions.

We recognize, as he has pointed out, that the kind of study he has performed would be much more difficult and perhaps impossible had he attempted to include these factors. We suggest that even were no alternative research strategies available, confidence in the conclusions of such a study must be severely weakened when the difficulties and uncertainties are realized. We repeat that it is better to face up to the gaps in our scientific knowledge than to make conclusions based on faulty and incomplete analyses.

Part of the problem is the choice of the study design. There are other research strategies that eliminate by their design some of the sources of error Dr. Schimmel has attempted to cope with by statistical techniques alone.

The temporo-spatial strategy corrects for slow rhythms, seasonality, and weather by the direct use of control groups. For example, we compared two inner-city areas, Harlem and Bedford-Stuyvesant, which are almost identical in social and demographic variables, and which may be presumed to have similar weather conditions. These areas each contain stations of the New York City aerometric network, and it has been found that they differ in day-to-day variation of the pollution levels. Daily visits for respiratory illnesses (including asthma) to hospital emergency rooms in these areas were used as the health indices. We also reported a study[29] in which pollution variables were ignored initially, and instead were identified with days on which when extraordinarily large numbers of visits to emergency rooms for respiratory conditions (e.g., asthma) occurred. We found that on some occasions such extraordinary events occur simultaneously at many emergency rooms throughout the city, and we infer that on such days a common environmental factor—pollution or weather, for example—must have appeared over the entire city. A search for the common factor on the days in question may then be instituted. Such an approach does not start with an a priori hypothesis as to which environmental factor or pollutant is harmful to health, but rather serves as a screen to identify possible environmental conditions related to acute health effects.

Summary

We suggest that the methodological weaknesses of Dr. Schimmel's study design are so severe that no conclusion may be safely drawn from it. Specifically, we submit that his main conclusion, that health effects attributable to air pollution have not declined while sulfur dioxide in the ambient air has declined significantly, is not adequately supported by his analysis and should not therefore be a basis of decisions on air-quality standards or what kind of fuel to burn.

As Dr. Schimmel has expressed a view that the criticism of his work made by our group is not based on scientific grounds, but rather on our "proenvironmental bias" and our unrealistic demand that a relaxation of standards not be undertaken in the absence of proof that sulfur dioxide is harmless, we would like to make clear what our position is for the record.

Our critical views of the methodology used by Dr. Schimmel began when one of us heard Dr. Schimmel's paper at an Atlantic City meeting of the Air Pollution Control Association, published in the *Journal of the Air Pollution Control Association* in 1972.[1] The paper showed that, after correcting for seasonality and several other factors,

> The estimated average daily excess deaths ranged from 18.2 to 36.74 with an intermediate estimate of 28.63. This latter figure would represent about 10,000 deaths a year which would not have occurred at the time they did, if there had been no pollution on the day of death or on immediately preceding days. In percentage terms this represents 12% of the over half-million deaths which occurred during these six years.[1]

We felt that this result needed careful scrutiny. Many of our criticisms of his current diametrically opposite conclusions were equally applicable to that paper. One of us discussed a paper reporting results of the CHESS studies presented to the Health Effects Section of the Air Pollution Control meeting in June 1972, and was strongly critical of the methodology of that paper, which appeared to demonstrate adverse health effects of air pollution.[30]

In response to one of our previously published criticisms, the same issue was raised by Dr. Schimmel. We stated our position at that time (in 1975) as follows:

> While the considerations of fuel costs and national energy self-sufficiency are significant ones at this time, and must enter into any decision on what air quality standards to set for sulfur dioxide along with considerations of health effects of sulfur dioxide, we dissent strongly from Drs. Schimmel and Murawski's conclusions that a scientific basis exists for assessing the latter and concluding they are negligible.

We are doing our best to separate purely scientific questions from questions of public policy. Our position is still that quoted from our previous criticism. We believe that the strategy of this kind of study is not capable of yielding the answers needed either as to the health effects of sulfur dioxide or the risks of burning fuel containing more sulfur. We wish that more definitive answers to these questions were forthcoming because we recognize the social importance of having answers and that it is sometimes necessary to make decisions on the basis of limited information. But the degree of confidence we have in this study is so small that it would be better openly to admit our scientific ignorance than to gloss over it.

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